WBCs, Neutrophils to Lymphocytes, Monocytes to Lymphocytes and Platelets to Lymphocytes Ratios to Predict the Severity of Covid-19 Cases among Intensive Care Unit Patients

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Abstract

Introduction: On March 2020, the World Health Organization (WHO) introduced the disease of Coronavirus 2019 (COVID-19) as a pandemic disorder. Although Covid-19 has spread rapidly causing serious health problems and might lead to death no effective treatment has discovered yet, the detection of reliable and useful prognostic markers is helpful to predict the severity and prognosis among Covid-19 patients. Thus, the current study aimed to assess and compare the level of WBCs, lymphocytes, neutrophils, monocytes and platelets in Covid-19 patients and control group. This study also evaluated neutrophils to lymphocytes, monocytes to lymphocytes and platelets to lymphocytes ratio.

Methods: This is a retrospective study included 385 participants 350 of which were confirmed COVID- 19 cases. Whereas the control group include 35 healthy individuals.

Results: The result of this study showed a significant increase in total WBCs count, significant low lymphocytes count and significant high neutrophil count in Covid-19 patients admitted in intensive care unit (ICU) compared to the control group. The result of this study also reported significantly (P < 0.0001) higher values for neutrophil-to-lymphocyte ratio (NLR), monocytes-to-lymphocyte ratios (MLR) and platelet-to-lymphocyte ratio (PLR), in Covid-19 patients admitted in ICU.

Conclusion: Based on the findings of this study, which revealed significant changes in a number of blood cells among Covid-19 patients admitted to ICU, it is suggested that level of WBCs, NLR, MLR and PLR can be use as a useful prediction marker to predict the severity of Covid-19 cases in ICU.

Keywords: White Blood Cells; Neutrophils to Lymphocytes Ratio; Monocytes to Lymphocytes Ratio and Platelets to Lymphocytes Ratio; Covid-19

Abbreviations

NLR: Neutrophil-to-lymphocyte Ratio; MLR: Monocytes-to-lymphocyte Ratio; PLR: platelet-to-lymphocyte Ratio; ICU: Intensive Care Unit

Introduction

On March 2020, the World Health Organization (WHO) introduced the disease of Coronavirus 2019 (Covid-19) as a pandemic and a member of the Coronavirus family. Covid-19 found to be associated with different sign and symptoms ranging from the head-

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ache, fever, usual cold, fatigue, dry cough to respiratory failure, interstitial pneumonia and septic shock [1]. Such serious clinical manifestations are often develop rapidly, unexpected and might be fatal if not managed and treated urgently [1]. Individuals with chronic disease including hypertension, cancer, cardiovascular, pulmonary disorder and diabetes have been classified as high risk group [2,3]. Dysfunction of the immune cells as well as abnormal response were detected in patients with severe Covid-19, suggesting low concentration of neutrophil (NETs) within tissues [4,5]. Moreover, it has been reported that the low level of leukocytes or impaired their function could result in mild to severe health problem and disorders [6].

A number of several laboratory investigations have been assessed to predict the severity and prognosis among hospitalized Covid-19 patients. Such of theses hematological laboratory tests are C-reactive protein (CRP), white blood cell (WBC) level, red cell distribution width (RDW), ratio of neutrophil (NETs) to lymphocyte, ratio of monocytes to lymphocyte and ratio of platelet to lymphocyte [7]. A recent study done in Saudi Arabia has found a significant reduction in the concentration of total WBC, neutrophil, lymphocyte and monocyte count among patients with Covid-19 [1]. Lagunas-Rangel has evidenced that neutrophil-to-lymphocyte ratio (NLR), an important marker of systemic inflammation and infection, which improve the inflammatory function in Covid-19 patients [8]. A retrospective study included the clinical data from 443 Covid-19 patients with non-severe and sever cases at Wuhan Forth Hospital, found that neutrophil-to-lymphocyte ratio, CRP and platelets were independent protective factors for patients with severe Covid-19 [9]. Another retrospective analysis performed on 72 Covid-19 hospitalized patients reported low lymphocytes and low white blood cell count in 54.2% and 20 27.8% patients respectively. Within the same study, it has been detected that leukocyte, neutrophil level and neutrophil-lymphocyte ratio (NLR) were significantly high in non-severe patients compared to patients with severe cases [10]. Udugama and colleagues found that age, WBC count and CRP level were significantly higher in severe Covid-19 patients compared to other patients, however, lymphocyte concentration was significantly lower [11]. The length of hospital stay and prognosis of the disease were noticed to be highly associated with increase in platelets-to-lymphocyte ratio PLR level among 30 hospitalized patients with confirmed Covid-19 in Huizhou Municipal Central Hospital [12].

Aim of the Study

The aim of this study was to assess the WBC indices, including total WBC level, neutrophil level, lymphocyte level, monocyte level and platelets count. This study was also evaluate the ratio of the following: neutrophils to lymphocytes, monocytes to lymphocytes and platelets to lymphocytes among Covid-19 cases at intensive care unit in Saudi Arabia.

Materials and Methods

This is a retrospective study included 350 confirmed Covid-19 adult patients who hospitalized in government hospitals at the Western region of Saudi Arabia. Out of these 350 patients, 197 (56%) were mal and 153 (44%) female. The majority were Saudi and aged above 40 year (Table 1). All patients were diagnosed by quantitative Polymerase Chain Reaction (qPCR) on collected nasopharyngeal swab. As the Saudi Ministry of Health criteria for intensive care unit admission, patients were symptomatic, a temperature of 38.5°C with a shortness of breath or decrease in mean arterial pressure below 60 mmHg. Most of ICU admitted patients were had a chronic disease including diabetics and hypertension.

Characteristics	Controls (n = 35) Median (95%CI)	COVID-19 case n = 350) Median (95%CI)	P-value
Age	64 (59-66)	64 (64-64)	0.1 NS
White blood Cells (WBC)	8 (7-9)	9.9 (9.2-10.4)	0.001*
Lymphocyte	3.3 (3.2-4.0)	1.3 (1.2-1.4)	< 0:0001**
Platelet	360 (320-390)	279 (265-297)	< 0:0001**
Monocyte	0.7 (0.6-0.8)	0.59 (0.55-0.64)	0.3 NS
Neutrophil	4.0 (3.8-4.8)	7.5 (6.96-8.02)	< 0:0001**
NLR	1.15 (1.03-1.33)	5.3 (4.66-5.94)	< 0:0001**
MLR	0.19 (0.16-0.21)	0.41(0.37-0.44)	< 0:0001**
PLR	103.8 (93.8- 118.2)	207.9 (190.3-224.8)	< 0:0001**

Table 1: Clinical characteristics and laboratory results of the control and covid-19 cohorts.

Patients demographic data were collected and results of hematological laboratory investigations were also recorded from

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the electronic medical records of the hospitals. Control group was including 35 healthy individuals 18 (51.4%) females' participants and 17 (48.6%) males) aged 40 year and older. Complete blood count (CBC) for the control group was recorded and the interested median ratios were calculated (Table 1). All personal identification information were kept highly confidential.

Ethical approval

The ethical approval for this study was obtained from the Research Ethics Committee at the College of Applied Medical science at Taif University as well as the Ethics Committee of the Ministry of Health (number:HAP-02-T-067). The study was conducted from March to September 2019.

Statistical analysis

Statistical analysis were carried under R statistical environment. Data distribution was tested using Shapiro-Wilk test of normality package. Non parametric version of t-tests to examine significance difference in median values was done using Wilcox test.

Results

The data set consists of 385 participants 350 of which were confirmed Covid-19 cases admitted in ICU. There 153 females' patients (43.7%) and 197 male patients (56.3%) (Figure 1). Whereas the control group include 18 (51.4%) females' participants and 17 (48.6%) males.
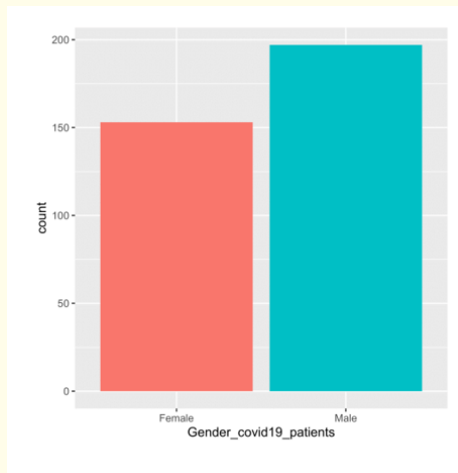
Table 1 shows clinical characteristics and laboratory results of the control group and Covid-19 cases as well as the median values with 95% confidence interval and its significance differences. Equal medians of both patients' and control group age therefore no significance difference was attained (Figure 2).
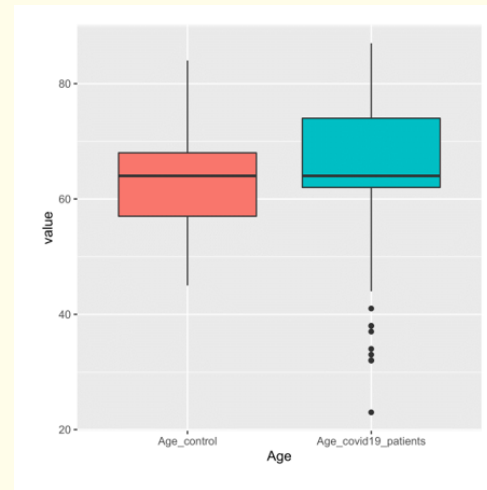

Figure 2: Age of control and Covid-19 patients.

Boxplot of Age for control and Covid-19 patients, where top and bottom lines represent the maximum and minimum values, the top and bottom of each box represent the first quartile (Q1) and third quartile (Q3) where the line inside each box is the median (second quartile Q2), dots blew are outlier value.

The Covid-19 patients in ICU had median of white blood cells (WBCs) count 9.9 which was significantly higher compared to the control group (p - 0.001). Figure 3A shows the Boxplot of white blood cells count of control and COVID-19 patients, where top and bottom lines represent the maximum and minimum values, the top and bottom of each box represent the first quartile (Ql) and third quartile (Q3) where the line inside each box is the median (second quartile Q2), dots above are outlier values. The patients' group were showing great number of outlier values compared to the control group.

The result of this study showed that the Covid-19 patients in ICU had a median lymphocyte of 1.3 (Table 1) which was significantly lower compared to the control group (P < 0.0001). It is also
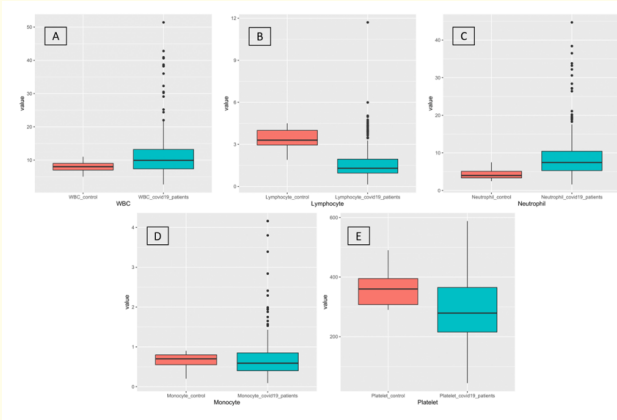

Figure 1: Distribution of Covid-19 patients' gender.

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Figure 3: WBC, neutrophil, lymphocyte, monocyte and platelets of control and Covid-19 patients.

Boxplot of WBC, neutrophil, lymphocyte, monocyte and platelets for control and Covid-19 patients, where top and bottom lines represent the maximum and minimum values, the top and bottom of each box represent the first quartile (Q1) and third quartile (Q3) where the line inside each box is the median (second quartile Q2), dots above are outlier value.

worth mentioning the large number of outliers among Covid-19 patients (Figure 3B). On the other hand, the median of neutrophil counts was significantly lower in control in comparison with Covid-19 patients 4.0 vs 7.5 (Table 1 and figure 3C). The current study also assessed the monocytes level among both groups, no significant differences were observed (Table 1 and figure 3D). In addition, statistically significant differences were observed in the platelet count (p < 0.0001). Covid-19 patients admitted in ICU had a median of 279 compared to 360 for the controls (Table 1). No outliers' values were recorded of platelet counts for both controls and cases (Figure 3E).

Comparisons of neutrophil-to-lymphocyte ratios (NLR) between the different groups, showed values for control compared to Covid-19 patients significantly (P < 0.0001) lower (1.15 vs 5.3) (Figure 4A). The Covid-19 patients had a median monocytes-to-lymphocyte ratios (MLR) of 5.3 (Table 1) which was significantly (P < 0.0001) higher compared to the control group (0.19). It is also

worth mentioning the large number of outliers of Covid-19 patients (Figure 4B). A similar image was also observed for platelet-to-lymphocyte ratio (PLR), where the Covid-19 patients had a median PLR of 207.9 (Table 1 and figure 4C) which was significantly (P < 0.0001) higher compared to the control group (103.8). It is also worth mentioning the large number of outliers among Covid-19 patients.
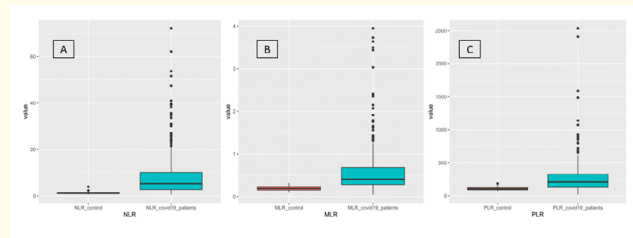

Figure 4: NLR, MLR, PLR of control and Covid-19 patients.

Boxplot of NLR, MLR, PLR of control and Covid-19 patients for control and Covid-19 patients, where top and bottom lines represent the maximum and minimum values, the top and bottom of each box represent the first quartile (Q1) and third quartile (Q3) where the line inside each box is the median (second quartile Q2), dots above are outlier value.

Discussion

Although Covid-19 has spread rapidly since 2019 and no effective treatment has discovered yet, the detection of reliable and useful prognostic markers is helpful to predict the severity and prognosis among Covid-19 patients [13]. Thus, the current study aimed to assess and compare the level of WBCs, lymphocytes, neutrophils, monocytes and platelets in Covid-19 patients and control group. This study also evaluated neutrophils to lymphocytes, monocytes to lymphocytes and platelets to lymphocytes ratio.

A significant increase in WBCs in Covid-19 patients admitted in ICU was reported in the present study. Unlike this study, Xu (2021) found out a lower WBC concentration in patients with Covid-19 compared to healthy individuals [14]. On the other hand, significantly higher WBC count was reported among 51 Covid-19 patients in ICU [15].

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A research study suggesting that the inhibition on cellular immune function has been associated with the reduction in the level of lymphocytes, which coronavirus may cause [16]. The results of this study showed a significant low level of lymphocytes count and a significant high level of neutrophil counts in Covid-19 patients who admitted in ICU compared to the control group. Similar to this study, Eslamijouybari., *et al*. reported that lymphocyte counts were significantly lower and neutrophil counts were significantly higher in the Covid-19 positive cases compared to healthy persons [17]. Another more recent study found that lymphocyte and neutrophil counts were significantly low among Covid-19 patients, on admission [18].

Regarding monocytes count, some research study suggesting that monitoring this type of cell can be a simple and important prediction tool to identify the severity and risk of progression of Covid-19 [19]. The result of monocytes level in this study showed no significant differences among both groups. However, a study done in Italy detected low lymphocytes and monocytes count in the peripheral blood examination for Covid-19 patients [20]. Another study reported significantly less monocytes level and abnormal vacuolization under the microscopic examination for Covid-19 patients, who admitted in ICU [15].

The positive correlation has been found between the platelet level with the length of stay-in hospital among Covid-19 patients [21]. Jayanthi and Tulasi, in their prospective observational study showed that the decreased in platelet count associated with increased complication rate as well as study duration of hospital [22]. In this study, statistically significant decrease were observed in the platelet count (p < 0.0001) in Covid-19 patients admitted in ICU. Similar to this study's result, a study reported a significant decrease in platelet count in patients with severe Covid-19 [23].

Focusing on neutrophil-to-lymphocyte ratio (NLR), monocytes-to-lymphocyte ratios (MLR) and platelet-to-lymphocyte ratio (PLR), in this study, all three ratios were found to be significantly (P < 0.0001) higher in Covid-19 patients admitted in ICU. In previous, a cross-sectional study has been assessed 527 patients with Covid-19 and found that neutrophil-to-lymphocyte ratio (NLR) was two times higher in the Covid-19 patients compared to controls, which is in line with this study [17]. The data were in line with this study's results reported in several research studies in different countries: Turkey [24], Saudi Arabia [1] and China [25].

Conclusion

The results of this study showed significant changes within the level of different parameters. Such of these are WBCs counts, lymphocytes, neutrophils and platelets level. In addition, statistically significant increase were detected on NLR, MLR and PLR. Thus, this study suggested that assessment of WBCs, NLR, MLR and PLR can be a useful prediction marker to predict the severity of Covid-19 cases who admitted to ICU.

Limitations of the Study

This study has number of limitations including the sample size was small and, hence, further, larger studies are warranted. Moreover, the study performed among limited hospital in the Westren region of Saudi Arabia, more area should be included.

Declarations

The authors declare that they have no conflict of interests.

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